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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/086,738 | 03/04/2002 | Atsushi Miyawaki | P22042 | 2194 |
| 7055 | 7590 | 07/26/2004 | EXAMINER | |
| GREENBLUM & BERNSTEIN, P.L.C. 1950 ROLAND CLARKE PLACE RESTON, VA 20191 | | | | SLOBODYANSKY, ELIZABETH |
| | | ART UNIT | | PAPER NUMBER |
| | | 1652 | | |

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|-----------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/086,738 | MIYAWAKI ET AL. | |
| | Examiner | Art Unit | |
| | Elizabeth Slobodyansky, PhD | 1652 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 17 May 2004.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 5-21 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-4 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 04 March 2002 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 5/28/02; 7/26/02.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

The amendment filed May 17, 2004 amending claims 1, 4-6, 9, 11, 19 and 21 has been entered.

The substitute Sequence Listing and the computer readable form thereof filed May 17, 2004 have been entered.

Claims 1-21 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-4, in the reply filed on May 17, 2004 (page 15) is acknowledged. The traversal is on the ground(s) that "there is no serious search burden" (page 15, 3rd paragraph) and "'an appropriate explanation" must be advanced by the Examiner as to the existence of a "serious burden" if a restriction were not required" (*ibid*, 2nd paragraph). This is not found persuasive because coexamination of each of additional groups would require search of class/subclasses unnecessary for the examination of the elected claims such as at least class 435 subclasses 4, 252.3, 810 and class 536 subclasses 23.4, 23.5 in addition to the additional sequence search. Furthermore, the examination of additional Groups would require divergent considerations. In addition, the specification provides no clear description of the sequences defined by SEQ ID NOs: rendering it difficult to evaluate the scope of the invention prior to its complete examination. Furthermore, the claims are

unclear as explained below. Therefore, coexamination of each of these additional inventions would require a serious additional burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups II-XIII, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 17, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the fused fluorescent protein" in line 11. There is insufficient antecedent basis for this limitation in the claim. Similarly, claims 2 and 3. Claim 4 is rejected as dependent from claim 1.

For the purpose of this examination claim 1 is construed as drawn to a recombinant fluorescent protein comprising C-terminal fragment of a fluorescent protein, a linker and a N-terminal fragment of a fluorescent protein wherein the fusion of said recombinant fluorescent protein with a Ca²⁺ binding protein and its target peptide results in a fluorescent fusion protein having Ca²⁺ dependent

fluorescence. However, no fusion protein comprising said recombinant fluorescent protein is claimed.

Further, the claims recite green fluorescent protein (GFP), a yellow fluorescent protein (YFP), a cyan fluorescent protein (CFP), a red fluorescent protein and a blue fluorescent protein (BFP). It is unclear which GFPs other than *Aequorea victoria* GFP are encompassed by the term “green fluorescent protein”. It is further unclear which mutations have YFP, CFP or BFP relative to GFP (see page 27, 2nd paragraph, starting with “Most YFPs”, emphasis added). Similarly, the terms “CFP” and “BFP”. It is not defined in the specification which sequences are encompassed by the term “red fluorescent protein”.

In claim 3 the expression “excitation of a wavelength” is unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a fluorescent protein in which the amino and carboxyl portions are interchanged and connected via linker. The claims encompass a genus of any of green fluorescent protein (GFP) or its mutants, a

yellow fluorescent protein (YFP) or its mutants, a cyan fluorescent protein (CFP) or its mutants, a red fluorescent protein or its mutants and a blue fluorescent protein (BFP) or its mutants. The genus of naturally occurring GFPs is a diverse genus comprising proteins having different amino acid sequences and chromophores from any species including any species of *Aequorea*. YFP, CFP, BFP and red fluorescent protein are mutants of *Aequorea victoria* GFP. Mutants of these proteins are not limited by structure. Thus, the claims encompass a genus of fluorescent proteins of any structure in which the amino and carboxyl portions are interchanged and connected via linker. When said fluorescent protein is fused with any Ca^{2+} binding protein and its target peptide, the resulting fluorescence is Ca^{2+} dependent. The specification teaches "repcams" based on circularly permuted YFP (cpYFP) which was fused with CaM and M13 (26 residue peptide derived from a CaM binding region of skeletal muscle myosin light chain kinase).

However, in the instant case, there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only several species within the genus wherein the correlation between the structure and

function (fluorescent characteristics) is neither known in the art nor disclosed by the specification.

Thus, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reprints of the invention, does not reasonably provide enablement for a fluorescent protein of any structure in which the amino and carboxyl portions are interchanged and connected via any linker that is fused with any Ca^{2+} binding protein and its target peptide emits a Ca^{2+} dependent fluorescence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-4 recite a fluorescent protein of any structure. There are no limitations on the stricture of Ca^{2+} binding protein and its target peptide as well. The specification teaches that the pericams of the invention have been found empirically (pages 24, 2nd paragraph; pages 25, 27-33). All pericams of the invention are based on YFP and CaM and M13. However, the claims encompass diverse structures that may not have any similarity to the instant pericams. It is *a priori* unpredictable as to which other molecules in combination with cpYFP will produce Ca^{2+} dependent fluorescence and vice versa it is *a priori* unpredictable as to which other circularly permuted fluorescent proteins fused with CaM and M13 will produce Ca^{2+} dependent fluorescence.

The specification does not support the broad scope of the claims which encompass fluorescent constructs of any structure that emit Ca^{2+} dependent fluorescence because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the specific requisite fluorescent activity of the protein of the instant invention; (B) the general tolerance of said protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired fluorescent function when used in a fusion with any Ca^{2+} binding protein and its target peptide; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Despite knowledge in the art to produce mutations in proteins, the specification fails to provide guidance as to where, and what type of (i.e., what

amino acid to substitute into, add to or delete from the known sequence), changes in amino acid residues will result in a desired biological activity. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in a certain activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited.

Furthermore, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

Therefore, one of ordinary skill in the art would require guidance, beyond that provided, in order to make a fluorescent protein that emits Ca^{2+} dependent fluorescence when fused with any Ca^{2+} binding protein and is target, other than pericams of the instant invention in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by Nagai et al.

Nagai et al. (form PTO-1449 filed July 26, 2002, reference 1, PNAS, 98, 3197-3202, 13 March 2001) teach the pericams of the instant invention (entire article, especially Figure 1, Table 1).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Baird et al.

Baird et al. (form PTO-1449 filed May 28, 2002, reference 6) teach circular permutations of EGFP, ECFP and EYFP wherein the original N- and C termini were connected with the hexapeptide GGTGGS (page 11242, 2nd column- page 11243, especially Figure 1a). These circularly permuted mutants will emit Ca²⁺ dependent fluorescence when fused with CaM and M13.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

July 21, 2004